REMARKS

Upon entry of this amendment, claims 32, 35-39, 42, 45-49, 52-55, 84 and 89-90 are pending. Claims 32, 35, 36, 42, 45, 46, 52-54, 84 and 89 have been amended. Support for these amendments can be found at, *e.g.*, page 4, lines 26-29; page 9, lines 27-28; and page 21, lines 10-24. Thus, no new matter has been added.

Claim Rejections -- 35 U.S.C. § 112

Applicants note that the rejections of claims 32-55, 84 and 85 under 35 U.S.C. § 112, first and second paragraph, have been withdrawn.

Claim Rejections -- 35 U.S.C. § 102

Claims 32, 35, 42, 45 and 84 remain rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,306,388 ("Nair"). The Examiner states that "in the absence of the evidence that the use of hybrid cells produces a population of structurally distinct immune effector cells, Nair et al. anticipate the instant claims." (See Office Action, page 3). To rebut this assertion, Applicants file herewith a Declaration under 37 C.F.R. § 1.132, by Donald Kufe, M.D. ("Kufe Declaration"), one of the named inventors of the instant application.

As noted by Dr. Kufe, the population of educated, antigen-specific cytotoxic immune effector cells of the present invention are structurally, immunologically, and biochemically distinct from the effector cells disclosed by Nair for at least the following reasons. The educated, antigen-specific cytotoxic immune effector cell population of the present invention contains $CD4^+$ immune effector cells and $CD8^+$ immune effector cells, because the hybrid cells express both Class I and Class II MHC molecules. In contrast, the population of effector cells disclosed by Nair, by virtue of their being produced by endogenous proteins, which are presented by Class I MHC molecules, is only $CD8^+$. (See Kufe Declaration, ¶ 5). The Nair effector cells are not $CD4^+$. (See Kufe Declaration, ¶ 5). In fact, Dr. Kufe notes that, because the immune response is amplified in a population of cells that contains cells that express CD4 as well as cells that express CD8, the antigen-specific cytotoxic immune effector cells of the present invention are immunologically, biochemically, and patentably distinct from the effector cells disclosed by Nair. (See Kufe Declaration, ¶¶ 4 and 5). Therefore, because the hybrid

cells of the instant application produce a distinct population of immune effector cells, Nair cannot anticipate the instant claims, and this rejection should be withdrawn.

Claims 32, 35, 42, 45 and 84 remain been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,156,307 ("Granucci"). The Examiner states that "in the absence of the evidence that the use of hybrid cells produces a population of structurally distinct immune effector cells, Granucci et al. anticipate the instant claims." (See Office Action, page 4).

Applicants note that the Kufe Declaration demonstrates that the population of antigen-specific cytotoxic immune effector cells of the present invention are structurally, immunologically, and biochemically distinct from the effector cells disclosed by Granucci for several reasons. (See Kufe Declaration, ¶ 6).

First, as stated above, the pending claims have been amended herein to specify that the immune effector cells are cytotoxic. In contrast, Granucci does not teach or suggest cytotoxic immune effector cells. (See Kufe Declaration, ¶ 6). It is well known that cytotoxic T cells require two signals to mature: the interaction with an MHC class I antigen, and IL-2, which is normally produced by nearby T helper cells. Granucci does not provide for T helper cells or another source of IL-2. Therefore, the effector cells produced by Granucci are not cytotoxic. (See Kufe Declaration, ¶ 6).

Second, the population of cytotoxic immune effector cells of the present invention contains both $CD4^+$ immune effector cells and $CD8^+$ immune effector cells. However, the effector cells disclosed by Granucci can be loaded with antigens which are associated with either Class I or Class II MHC molecules, but not with both. (See Kufe Declaration, ¶ 6). Loaded polypeptide or protein antigens are presented by Class II MHC molecules only, while certain peptides are associated with Class I only. Id. According to Dr. Kufe, there is an enhanced immune response observed in populations containing cells expressing CD4 as well as cells expressing CD8 (due to the interaction between $CD4^+$ cells and $CD8^+$ cells). (See Kufe Declaration, ¶ 4). In fact, Granucci teaches away from the educated immune effectors of the invention-- stating that it is not necessary to use fusions to educate immune effector cells. (See, *e.g.*, Granucci col. 4, line 56 to col. 5, line 34; Kufe Declaration, ¶ 7). As Dr. Kufe notes, the expression of $CD4^+$ and $CD8^+$ by cells of the claimed population of cytotoxic immune effector cells renders these cell populations of greater use in human cancer vaccines than the effector

cells disclosed by Granucci, which do not exhibit such an enhanced immune response. (See Kufe Declaration, ¶ 4).

Therefore, as Granucci fails to teach or suggest all of the limitations of the claimed invention, this rejection should be withdrawn.

Claim Rejections -- 35 U.S.C. § 103

Claims 32, 35-39, 42, 45-49, 52-55, 84, 89, and 90 have been rejected under 35 U.S.C. § 103(a) as being obvious over Granucci in view of WO96/30030 ("Moser"). The Examiner states that "as long as the combined teachings of Granucci et al and Moser et al disclose a population of such antigen-specific immune effector cells, the claim limitations are met regardless of how the cells are made." (See Office Action, page 5). Applicants traverse.

First, one of ordinary skill in the art would not be motivated to use the cell fusion technique of Moser to overcome the limitations of Granucci in order to obtain the educated cytotoxic immune effector cells of the invention. (See Kufe Declaration, ¶ 7). As noted above, the immune effector cells disclosed by Granucci can be loaded with antigens which are associated with either Class I or Class II MHC molecules, but not with both. As noted by Dr. Kufe, loaded polypeptide or protein antigens are presented by Class II MHC molecules only, while certain peptides are associated with Class I only. (See Kufe Declaration, ¶ 6). Moreover, Granucci teaches that it is not necessary to use fusions to educate immune effector cells. (See, *e.g.*, Granucci col. 4, line 56 to col. 5, line 34; Kufe Declaration, ¶ 7). Because Granucci teaches away from fusions, the ordinarily skilled artisan would not be motivated to use the fusions of immortal tumor cells from an autologous tumor with allogeneic dendritic-like cells described in Moser (See, *e.g.*, Moser abstract) in order to educate immune effector cells. Thus, there would be no motivation to combine Moser and Granucci.

Second, even if one were to combine the cell fusion technique of Moser with the antigen loading technique of Granucci, one skilled in the art would not obtain the cytotoxic educated immune effector cells claimed in the instant invention, which express the B7 co-stimulatory polypeptide (also known as CD80). The interaction of B7 with CD28 (and CD152) is crucial in T-B cell communication leading to activation of T and B cells, respectively. Moser was unable to obtain either murine or human fused cells that express B7, even though Moser used B7 expressing-dendritic cells as a starting material (See, *e.g.*, Moser Tables 1 and 2; See Kufe

Declaration, ¶ 7). B7 expressed on APCs physically interacts with costimulatory polypeptide CD28 expressed on the surface of T cells, and Dr. Kufe notes that this interaction is crucial in T cell-APC communication that results in activation of T cells. (See Kufe Declaration, ¶ 7). Since the hybrid cells recited in the instant claims express B7 they are therefore more capable of educating T cells than the cells provided by Moser, which do not express this costimulatory polypeptide.

Therefore, because Granucci in view of Moser fails to teach or suggest all of the limitations of the claimed invention, this rejection should be withdrawn.

CONCLUSION

Based on the instant amendments and remarks, Applicants submit that this application is in condition for allowance and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact Applicants' undersigned attorney at the telephone number indicated below.

Respectfully submitted,

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